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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/[illegible]	07/[illegible]	[illegible]	[illegible]

EXAMINER	
[illegible]	
ART UNIT	PAPER NUMBER
1636	5

022930
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DATE MAILED: 04/26/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/359,300	Kumagai, et al.
Examiner	**Group Art Unit**
Gerald G. Leffers Jr.	1636

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

X Claim(s) *1-45* is/are pending in the application.

Of the above, claim(s) *1-44* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

X Claim(s) *45* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

X See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

X Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

X Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because sequences were set forth that lack sequence identifiers, no CRF was filed, no paper sequence was filed and no attorney statement was filed. These sequences include the sequences found in a number of the figures. If the Sequence Listing required for the instant application is identical to that of another application, a letter may be submitted requesting transfer of the previously filed sequence information to the instant application. For a sample letter requesting transfer of sequence information, refer to MPEP 2422.05. Additionally, it is often convenient to identify sequences in figures by amending the Brief Description of the Drawings section (see MPEP 2422.02).

Applicants are required to comply with all of the requirements of 37 CFR 1.821 through 1.825. *Any* response to this office action that fails to meet all of these requirements will be considered non-responsive. The nature of the noncompliance with the requirements of 37 C.F.R. 1.821 through 1.825 did not preclude the continued examination of the application on the merits, the results of which are communicated below.

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-27, drawn to methods of changing the phenotype or biochemistry of a plant, determining a change in phenotype or biochemistry in a plant and determining the presence of a trait in a plant, classified in class 435, subclasses 6, 410; class 536, subclass 23.1, 24.5.

II. Claims 28-29, drawn to methods of determining a trait in a plant in which the trait is associated with a GTP binding protein, classified in class 435, subclasses 6, 410; class 536, subclass 23.1, 24.5.

III. Claims 30-32 and 35-38, drawn to methods of identifying nucleic acids in a donor organism, classified in class 435, subclasses 6, 410, 468; class 536, subclasses 23.1, 24.5.

IV. Claims 33 and 35-38, drawn to methods of isolating human cDNAs, classified in class 435, subclasses 6, 91.1, 410, 468; class 536, subclasses 23.1, 24.5.

V. Claim 34, drawn to humanizing plant cDNAs, classified in class 435, subclasses 6, 91.1, 410, 468; class 536, subclasses 23.1, 24.5.

VI. Claims 39-44, drawn to methods of increasing crop yield, classified in class 435, subclasses 6, 410, 468; class 536, subclasses 23.1, 24.5.

VII. Claim 45, drawn to methods of generating a functional gene profile for an organism, classified in class 435, subclasses 6, 410, 468; class 536, subclasses 23.1, 24.5.

The inventions are distinct, each from the other because of the following reasons:

The inventions of Groups 1-VII are biologically and functionally different and distinct from each other and thus one does not render the other obvious. The methods of Groups I-VII comprise steps which are not required for the methods of the other groups: correlating one or more biochemical changes in an infected host plant to an uninfected plant (Group I), correlating the expression of a nucleic acid expressed in a plant to a biochemical or phenotypic change observed in the plant wherein the nucleic acid encodes a GTP-binding protein (Group II), sequencing the insert nucleic acid which yields the observed biochemical or phenotypic change (Group III), nucleic acid hybridization (Group IV), comparing amino acid sequences encoded by a plant cDNA to amino acid sequences encoded by a human cDNA (Group V), transiently expressing a nucleic acid in an antisense orientation to increase seed production (Group VI) and compiling a list of host and donor genes associated with a trait associated with an observed biochemical or phenotypic change in a plant (Group VII). The end results of the different methods are different: determination of a biochemical or phenotypic change in a host plant as a result of expression of a heterologous nucleic acid and determining traits associated with that change (Group I), determination of a trait in a plant in which the expressed nucleic acid encodes

a GTP-binding protein (Group II), identification of a nucleic acid in the donor organism which appears to be associated with a trait (Group III), isolation of human cDNAs (Group IV), "humanization" of a plant cDNA (Group V), generation of a plant with improved seed yield (Group VI) and compilation of a functional gene profile in both a donor and host organism (Group VII). Thus, the operation, function and effects of these different methods are different and distinct from each other. Therefore, the inventions of these different, distinct groups are capable of supporting separate patents.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, and because the search required for Group II (GTP-binding proteins, G-protein signal transduction pathways, etc.), Group III (different methods of identifying nucleic acids based on partial sequence), Group IV (methods of isolating nucleic acids), Group V (methods of humanizing heterologous coding sequences), Group VI (methods of increasing a crop yield) and Group VII (high through-put gene discovery methods) is not coextensive with any of the other groups, restriction for examination purposes as indicated is proper.

During a telephone conversation with Al Halluin on or about 3/7/00 a provisional election was made with traverse to prosecute the invention of Group VII, claim 45. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-44 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 45 of this application conflicts with claim 43 of Application No. 09/359,297 and with claim 43 of Application No. 09/359,305. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for

their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

Claim 45 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 43 of copending Application No. 09/359,297. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of claim 45 of the instant application is an obvious variation of the method of claim 43 in Application No. 09/359,297. Claim 43 of Application No. 09/359,297specifies that the nucleic acids (derived from any donor) are oriented, depending on how the claim is read (see below), either all in a positive sense orientation, negative sense orientation or a mixture of both orientations within the pool of nucleic acids expressed in the plant host. It is and was well known in the art at the time the invention was made (see Roninson et al, below) that expression of DNAs, in either orientation, having homology to endogenous plant genes may result in phenotypic changes due to alteration of the expression of the host gene. Claim 45 of the instant specification merely specifies that all of the donor nucleic acids be oriented in a single, positive sense orientation.

Likewise, claim 45 is also provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 43 of copending Application No. 09/359,305. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of claim 45 of the instant application is an obvious

variation of the method of claim 43 in Application No. 09/359,305. Both claims are directed towards a screening method in which heterologous nucleic acids are expressed in a plant host and any detectable biochemical or phenotypic change is associated with expression of a particular donor nucleic acid. It is and was well known in the art at the time the invention was made that expression of DNAs in a positive sense orientation which have homology to endogenous plant genes may result in phenotypic changes due to alteration of the expression of the host gene. Claim 45 of the instant application specifies that any organism can serve a the donor whereas claim 43 of Application No. 09/359,305 merely limits the donor organisms to plants.

These are provisional obviousness-type double patenting rejections because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 45 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 45 is vague and indefinite in that the metes and bounds of the phrase "..being in a positive sense orientation"are unclear. The concept of orientation of an insert within a vector is not well defined in the specification. The claims are written with open language with regard to the source of the DNA or RNA used to make the vector library, encompassing coding as well as non-coding/non-complementary sources of nucleic acid sequences. It is unclear whether the limitation of orientation within the vector is directed towards the source DNA or RNA (i.e. derived from coding or complementary sequences) or is in fact a functional limitation in which the expressed nucleic acids exert their influence by antisense or sense mechanisms. It would be remedial to amend the claim language to clearly indicate what is intended by the orientation limitation for each of the heterologous nucleic acid inserts in the vector library.

Claim 45 is vague and indefinite in that the metes and bounds of the term "functional gene profile" are unclear. The term is defined in the specification (page 35, lines 3-12) as "The collection of genes of an organism which code for a biochemical or phenotypic trait. The functional gene profile of an organism is found by screening nucleic acid sequences from a donor organism by over expression or suppression of a gene in a host organism. A functional gene profile requires a collection or library of nucleic acid sequences from a donor organism. A functional gene profile will depend on the ability of the collection or library of donor nucleic acids to cause over-expression or suppression in the host organism. Therefore, a functional gene profile will depend upon the quantity of donor genes capable of causing over-expression or suppression of host genes or of being expressed in the host organism in the absence of a

homologous host gene.". It is unclear from the claim language and from the definition given in the specification as to how many of the possible genes in an organism which "code" for a biochemical or phenotypic trait are required to be characterized by the claimed methods before a "profile" has been obtained. Would identification of only 2 genes of the many possible genes in either the host or donor organism which are associated with the determined phenotypic or biochemical change due to overexpression of heterologous nucleic acids in the host satisfy the criteria for a functional gene "profile" for that organism? The definition states that the functional gene profile will depend upon the quantity of donor genes capable of causing over-expression or suppression of host genes or of being expressed in the host organism in the absence of a homologous host gene, implying that the number of genes that needs to be characterized in order to generate a functional gene profile are all of the genes from an organism, host and/or donor, which are associated with a phenotypic or biochemical change due to expression of heterologous nucleic acids in the host. Would a "functional gene profile" be generated only when **all** of the genes from a donor or host organism which are associated with a biochemical or phenotypic change when heterologous nucleic acids are expressed in an organism are identified? If so, how would one know when all of the genes from either the host or donor organism which are associated with the biochemical or phenotypic change have been identified and the claim limitation has been met? It would be remedial to amend the claim language to clearly indicate how many of the possible genes from a donor or host organism associated with the determined

biochemical or phenotypic change need to be identified in order to satisfy the limitation of being a "profile".

Similarly, claim 45 is vague and indefinite in that it is unclear whether the functional gene profile necessarily includes identified genes associated with more than one trait associated with a biochemical or phenotypic change, or is necessarily limited to the identified genes associated with just one trait associated with a biochemical or phenotypic change. The definition given in the specification is directed towards a "collection of genes of an organism which code for **a** biochemical or phenotypic trait", implying that the collection of genes is associated with just one trait associated with a biochemical or phenotypic change observed upon expression of heterologous nucleic acids in a plant host. Step (h) specifies repeating the steps of (b) - (g), implying that multiple phenotypic or biochemical changes associated with multiple traits are necessarily included in the profile. It would be remedial to amend the claim language to clearly indicate whether a functional gene profile is limited to a single trait associated with one or more biochemical or phenotypic changes or whether the term refers to a collection of genes necessarily associated with multiple traits associated with multiple phenotypic or biochemical changes.

Claim 45 is vague and indefinite in that there is no explicit linkage between the vector of step (b) and the vector library of step (a). It would be remedial to amend the claim language to clearly indicate that the vector used to infect the plant host is a member of the vector library of step (a).

Claim 45 is vague and indefinite in that the metes and bounds of the phrase "..identifying an associated trait where a phenotypic or biochemical change occurs.." are unclear. The term "associated trait" does not appear to be well defined in the specification. What exactly is an "associated trait" in this instance and how does it differ from the biochemical or phenotypic change specified in the definition for a "functional gene profile"? How directly does the "associated trait" have to be associated with the biochemical or phenotypic change in order to satisfy the claim limitation? Does it have to be a function associated with a protein encoded by a nucleic acid homologous to the heterologous nucleic acid expressed in the plant host cell? It would be remedial to amend the claim language to clearly indicate what is intended by the term "associated trait" and how it differs from the biochemical or phenotypic change with which it is associated.

Claim 45 is vague and indefinite in that the metes and bounds of the phrase "..associated with the trait.." are unclear. The phrase is not clearly defined in the specification. How directly does the host or donor gene have to be linked to the trait which is itself associated with the observed biochemical or phenotypic change? For example, would a second gene encoding a second polypeptide which interacts with a first gene product from a first host or donor gene that yields the observed biochemical or phenotypic change, and which is itself required for the identified "trait", be considered to be "associated with the trait" associated with the biochemical or phenotypic change? Or would only the first gene encoding the first gene product be considered

to be "associated with the trait"? It would be remedial to more clearly indicate the functional linkage between the identified trait and a gene "associated with" the trait.

Claim 45 is vague and indefinite in that it is unclear whether steps (f) and (g) are optional or required steps in the claimed methods. If step (f) and step (g) are both required in order to practice either method, then how does performing the claimed method yield the result of step (h) in which a functional gene profile of the plant host **and/or** donor organism is compiled? It would appear that if both steps (f) and (g) are required, then a donor **and** host profile are automatically obtained. This question is an important one in that one can readily envision embodiments wherein it is not possible to directly attribute a linkage to **both** a host and donor gene (e.g. positive sense expression of a gene from a host with no homolog in the plant host and which no plant host gene can be shown to contribute to the observed biochemical or phenotypic change). In such an instance, would a gene in which an association to the observed biochemical or phenotypic trait can only be made for the plant host or for the donor be considered as a member of the functional gene profile? It would be remedial to amend the claim language such that it is clearly indicated whether both steps (f) and (g) are required in order for a gene to be considered a member of the functional gene profile, or whether only one of the two steps needs to be done in order for the identified gene to be considered a part of the profile.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 45 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of compiling a functional gene profile of an organism in which the vector library comprises inserts derived from known coding sequences (i.e. cDNAs or mRNAs) or their complementary sequences, does not reasonably provide enablement for such a method in which the vector libraries are derived from sources comprising non-coding sequences (e.g. gDNA, random synthetic sequences, etc.). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, predictability of the art, state of the prior art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

The nature of the invention is complex, involving the construction and utilization of expression vector libraries in which **all** of the heterologous, insert nucleic acid sequences are arranged in a positive sense orientation. The vector libraries of the invention are used to express nucleic acid sequences within a plant host cell with the aim of introducing detectable biochemical or phenotypic changes in the host cell upon expression. Such changes could

rationally be expected to be mediated by antisense suppression of endogenous genes, sense-mediated suppression of endogenous genes by expression of a heterologous nucleic acid having significant homology to an endogenous coding sequence and expression of a polypeptide from the heterologous nucleic acid having some activity within the host cell. The claim clearly stipulates that the orientation of the donor insert sequences for each member of the library is determined prior to the use of the library in the assay.

The breadth of the claim exacerbates the complexity of the invention. The claim encompasses any nucleic acid such as genomic DNA which comprises sequences which are not part of, or complementary to, a coding sequence. There is no limitation as to the size of the insert DNA, meaning that any sized fragment from any source can be used to construct the library.

The specification does not adequately define what is meant by the limitation of "positive sense" orientation, making its use in the rejected claims indefinite (see above). Does this limitation mean that the sequences are derived from a known source and in such a way that all of the insert nucleic acid sequences are known to be either complementary or coding sequences for an organism? Or does the orientation limitation refer to a functional definition for the inserted nucleic acid sequence, directed to how the insert DNA is observed to mediate an effect in the plant host upon being expressed? Beyond giving no adequate definition as to what the limitation actually means, the specification also provides no guidance on how to construct a vector library in which all of the sequences are oriented in the vector in the same way. Nor does the

specification provide guidance on how to determine whether the inserts within the library are oriented in the same way. The only working examples given in the specification are ones in which a cDNA library was constructed or in which a genomic DNA library was constructed without regard to orientation of the insert DNAs.

Methods are known within the art regarding the construction of cDNA libraries in which all or most of the insert coding sequences are oriented to express a functional mRNA. Methods are known within the art for directionally cloning a desired DNA sequence in a particular orientation within an expression vector. Methods are known within the art for determining if an expressed nucleic acid sequence can be translated into a polypeptide (positive sense expression). Methods are known within the art for determining if a given nucleotide sequence is complementary or homologous to a gene within an organism. The art is not necessarily predictable as to whether or not a random nucleotide sequence will function upon expression in a host in a positive sense fashion (e.g. positive sense gene suppression or encode a polypeptide) or a negative sense fashion (i.e. antisense gene suppression).

Given the complex nature of the invention in which the orientation all of the insert nucleic acids within the vector library are determined prior to the use of the library in the methods of the invention, the breadth of the claims which encompass donor nucleic acids from any source comprising non-coding, non-complementary sequences, the lack of guidance from the specification on how to construct such a library or determine the orientation of each member of the library, the lack of working examples or even an adequate definition of what the orientation

limitation means from the specification, and the lack of predictability of whether a random sequence from any source is derived from a coding/complementary sequence or is derived from a non-coding/non-complementary source, it would require undue and unpredictable experimentation to construct and use such a library when the donor nucleic acid sequences are derived from a source comprising non-coding/non-complementary sequences. Absent a meaningful definition of what the orientation limitation actually means, one would have to assume that a functional definition applies. In which case, in order to make the vector library required to practice the invention the skilled artisan would have to first express each member of the library in the desired host and determine for **each** member of the library if the heterologous nucleic acid was expressed, and if so whether it mediates a detectable effect on the host cell and how it mediates the effect (i.e. positive sense or antisense). Alternatively, one of skill in the art might be able to reasonably predict the mode of action for each member of the library by amplifying the nucleic acid insert for each vector within the library, sequencing the insert nucleic acid, determining the presence of translational start/stop codons and relative orientation to the vector promoter, compare the insert sequence to those known for the host organism and attempt to predict how the expressed nucleotide will exert an influence. It would thus require undue, unpredictable experimentation to make the vector library required to practice applicants invention in which all of the donor nucleic acids of the library are oriented in either a positive sense or antisense orientation when the source nucleic acid sequences are not already known to be either coding or complementary sequences. Thus, applicants claimed invention of a method

for compiling a functional gene profile in which the vector library used in the method comprises donor insert sequences which are all oriented in one direction and in which the donor sequences are derived from any source, is not considered to be fully enabled by the specification. Only in the case where the donor sequences are derived from nucleic acid sources having a defined orientation (i.e. cDNAs or mRNAs) is there a reasonable expectation of success in constructing a vector library in which each of the insert DNAs is oriented in a positive sense or antisense direction.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c)

Claim 45 is rejected under 35 U.S.C. 103(a) as being unpatentable over Peterson et al (A).

Peterson et al teach methods for generating and screening novel metabolic pathways featuring the expression of combinatorial expression libraries (apparently expressed in a positive sense orientation) in a selected host and screening for transformants which produce a desired product or exhibit a desired activity (Abstract, column 6). Peterson et al teach that the libraries are constructed from one or more species of donor organisms including microbes, plants and animals with the intention of generating random fragments of the genomes of donor organisms which comprise entire biochemical pathways, or portions thereof, and which may be reconstituted in the host organism (column 6, lines 34-64). Peterson et al teach that instances where a library from a single donor organism was used to identify clones in which an entire biosynthetic pathway was encoded by the transformed donor nucleic acid are and were known in the art (column 5, line 60 - column 6, line 26). The inventors teach that either DNA or RNA may be used as starting genetic material for constructing the libraries used in their invention and that the libraries can be cDNA libraries, genomic DNA libraries as well as mixed cDNA/gDNA libraries (column 30). Peterson et al also teach that the metabolic pathways of the donor organism may also interact with metabolic pathways resident in the host organism to generate novel compounds or compounds not normally produced by the host organism (column 6, line 60). Peterson et al provide several possible selection schemes to screen transformants for desirable traits, including the use of reporter molecules operatively linked to a chemoresponsive

promoter (column 7, line 38), or the use of indicator cell types embedded in a semi-solid matrix for selection of transformants which produce a desired product which affect the indicator cell type (column 7, lines 50-60). Peterson et al teach that the genetics and biochemistry of the metabolic pathway that leads to production of the novel compounds may be delineated by characterizing the genetic material that was introduced into the isolated clone by sequencing, mutation, expression and further rounds of screening (column 7, lines 60-65; column 12, lines 37-40). Peterson et al teach that novel activities and/or compounds may be produced by hybrid pathways comprising donor and host derived components. Peterson et al also teach that the target metabolic pathway modified by donor gene products may be native to the host organism (column 13, lines 30-37). Peterson et al teach that any host-vector systems known in the art may be used in their invention, including those featuring plants as the host (column 20, lines 55-62). Peterson et al list plant cells derived from Nicotiana or Arabidopsis as preferred embodiments for practicing their invention (column 21, lines 40-42). Peterson et al teach that inducible promoters can be used for expression of the donor nucleic acid sequences in the host organism and in fact are preferable in instances where the products of the expression library may be toxic (column 22, line 65-column 23, line 2). Peterson et al teach that the library can be replicated or amplified by any technique known in the art so that the library can be used multiple times (column 33, lines 24-30). Finally, Peterson et al teach the use of their method to identify several clones isolated from two different libraries (in the host *S. lividans* TK64) which display a

phenotype of producing products with antimicrobial activity in assays against several microbial species (Tables IV and V, columns 68 and 69, respectively).

It is unclear as to whether Peterson et al teach their method to be exclusively used with libraries derived from a plurality of donor organisms (e.g. the term "one or more donor species" is not well defined in the text). Also, Peterson et al do not explicitly teach that the identification of multiple clones (and their associated genes) displaying a particular phenotype results in a "functional gene profile". Peterson et al also do not explicitly teach the identification and sequencing of plant host genes associated with any of the observed biochemical or phenotypic changes in the plant host upon expression of heterologous nucleic acids in the host cells.

It would have been obvious to one of ordinary skill in the art at the time the invention was made that one could practice the method taught by Peterson et al to screen for clones comprising heterologous nucleic acids encoding an entire biochemical pathway, or parts thereof, from a library obtained from a single organism rather than a mixture of nucleic acids derived from a plurality of donor organisms because Peterson et al teach that such libraries from a single source have in fact been used in the art to isolate and identify genes involved in a particular biochemical pathway in the single donor organism. One would have been motivated to do so in order to receive the expected benefit of simplifying the construction of the donor library and/or to receive the expected benefit of using a library from a source having a particularly desirable property (e.g. production of a desirable class of compounds or having a desirable enzymatic activity).

It would have been further obvious to one of ordinary skill in the art to use the method taught by Peterson et al to identify and characterize as many different clones from the vector DNA library which yield particularly desired traits because Peterson et al teach that many such clones can be isolated from a library, that the libraries can be used again and again and that the identified clones can be characterized by sequencing (i.e. identification of the donor genes associated with the observed trait), mutational analysis, expression and further screening. One would have been motivated identify and characterize as many different clones yielding as many different desirable traits as possible (in effect generating a functional donor gene "profile") in order to receive the expected benefit of 1) obtaining a number of clones having desirable features (e.g. desirable enzymatic activities or products) and 2) understanding the donor components necessary to yield such desirable activities or products. Understanding the properties of the donor factors resulting in particular activities or products might allow the rational design of new donor/host combinations which might yield even more desirable products or activities.

Similarly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to also identify and characterize whichever host gene products might be involved in producing the observed trait (i.e. a desired activity or product) because Peterson et al teach that the combination of donor and host genes may be responsible for the observed trait (e.g. both donor and host gene products are involved in a novel biochemical pathway yielding the desired trait) and because methods of identifying and characterizing genes within a host organism required for a particular phenotype are and were well known in the art at the time the invention

was made. One would have been motivated to characterize host genes whose gene-products are associated with the desired traits (thus generating a host functional gene "profile") in order to fully understand the nature of the biochemical pathway leading to the desired trait. Understanding the properties of both the host as well as the donor factors resulting in particular activities or products might allow the rational design of new donor/host combinations which might yield even more desirable products or activities.

Absent any evidence to the contrary, there would have been a reasonable expectation of success in using the method taught by Peterson et al to identify a number of different clones from a single donor organism which yield one or more desirable phenotypes (i.e. production of a desired product or activity) upon expression of their insert nucleic acid sequences in a plant host, to identify/characterize both host and donor genes whose gene products are associated with the observed traits (thus generating a functional gene "profile" for both donor and host) and to subsequently utilize the information gained from such a screen to optimize production of one or more activities/products within the plant host.

Conclusion

No claims are allowed.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R.

§ 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald Leffers, Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on Monday through Friday, from about 8:00 AM to about 4:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than 24 hours after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott, can be reached on (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

G. Leffers, Jr.

Patent Examiner

Art Unit 1636

April 24, 2000

TERRY MCKELVEY
PRIMARY EXAMINER